

Variations Guidelines updated in accordance with Article 4 of the Variations Regulation in the context of a Marketing Authorisation Variation

What does the inclusion of Article 5 recommendations, related unforeseen variations, mean for applicants?

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Reference framework

Commission Delegated Regulation (EU) 2024/1701 updates how these Article 5, concerned “unforeseen variations”, are managed.

NEW

ART. 4
Added text

Strengthened Role of EMA and NCAs:

They shall report annually to the Commission on:

- **Recommendations for unforeseen variations (Art. 5)**
- **New resulting variation classifications**
- **Updates needed for inclusion in the Guidelines**

The Commission:

Shall, **without undue delay**, consider the reports and integrate them into the Guidelines, including:

- New classification of variations
- Necessary updates to the Guidelines

Electronic publication of the Guidelines: The Commission **may publish:**

- An updated electronic version on its website. This version **may include necessary updates and new classifications** before the regular revision, to improve access to information.

Reference framework

Commission Delegated Regulation (EU) 2024/1701 updates how these Article 5, concerned “unforeseen variations”, are managed.

MAH may request a recommendation on the classification of the variation as follows:

From the **EMA** → for the centralized procedure

From the **NCA of the concerned Member State** → for Decentralized Procedure (DCP) and Mutual Recognition Procedure (MRP)

From the **NCA of the reference Member State** → for national procedure

ART. 5
Amended
text

- Recommendations issued by the Agency, Member States, and NCAs: Should lead to a **new classification of the variation.**



- The recommendation that results in a new classification of variation **must be consistent with the Guidelines and shall be regularly integrated in the Guidelines.**

Commission Delegated Regulation (EU) 2024/1701

CHANGES AND REQUIREMENTS

Most of the historical recommendations of Article 5 but not all of them, have been included in the revised Variations Guide. Some were so specific to the case that they did not warrant creating another scope.

EMA: Annual EMA reporting obligation.

Commission: is now required to assess and integrate recommendations without delay.

Stricter and detailed justification for any remaining unclassified variation shall be provided.

IMPACT

The variation Guidelines now explicitly cover several cases that previously required Article 5 interpretation.

Systematic integration of new scientific and technical advances into classification, reducing uncertainty for MAH

Unforeseen variations should quickly become “foreseen” through updated Guidance.

Article 5 is less frequently used, but when needed, they require stronger justification.

Integration of Article 5 Recommendations European Commission Guidelines (C/2025/5045)

FROM REGULATION TO GUIDELINES

Guidelines have been updated in accordance with Art. 4 of the Variations Regulation, incorporating the Agency's recommendations for managing unforeseen variations and their new classification



A number of previous Article 5 recommendations addressing unforeseen variations **has been formally incorporated into the revised Guideline.**

Dynamic and continuously updating: This allows for adaptation to new regulatory rules, scientific and technical advances and emerging post-authorisation needs.



More clarity and predictability: Ensures the Guideline matches the new lifecycle-oriented approach to medicinal product variations.

Revised ANNEX: Changes in Categories, Conditions & Documentation to reflect **scientific & technical progress and practical experience gained**



Incorporating some previous Article 5 recommendations into the ANNEX of the revised Guideline

Chapter	Classification	Type	Previous unforeseen variations	Topic/Scope of changes	Specific variation
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Q	Q.I.a.2.e	IA	B.I.a.2.z	Change in the manufacturing process of the active substance	Deletion of a manufacturing process of the active substance
Q	Q.I.a.4.f	IA	B.I.a.4.z	Change to in-process tests or limits applied during the manufacture of the active substance	Minor change of an analytical procedure for an in-process test
Q	Q.I.b.1.k	IB	B.I.b.1.z	Change in the specification attribute and/or acceptance criteria of an active substance, starting material/reagent/intermediate/ used in the manufacturing process of the active substance	Change in the testing of specification attribute, from routine to non routine testing (skip or periodic testing)
Q	Q.I.c.1.d	IA	B.I.c.z	Change in immediate packaging of the active substance	Deletion of one of the authorised bulk or final containers
Q	Q.I.c.4	IA	B.I.c.z	Change of a secondary packaging component of the active substance (including replacement or addition), when mentioned in the dossier	
Q	Q.II.b.3.e	IB	B.II.b.3.z	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	Change in the holding time of an intermediate or bulk product used in the manufacture of the finished product
Q	Q.II.b.5.f	IA	B.II.b.5.z	Change to in-process tests or limits applied during the manufacture of the finished product	Minor change of an analytical procedure for an in-process test

Incorporating some previous Article 5 recommendations into the ANNEX of the revised Guideline

Chapter	Classification	Type	Previous unforeseen variations	Topic/Scope of changes	Specific variation
Q	Q.II.c.4.c	IA	B.II.c.4.z	Change in synthesis, manufacturing or recovery of an excipient (when described in the dossier)	Deletion of one manufacturing process of an excipient
Q	Q.II.d.1.i	IB	B.II.d.1.z	Change in the specification attribute and/or acceptance criteria of the finished product	Change in the testing of specification attribute, from routine to non routine testing (skip or periodic testing)
Q	Q.II.e.6.e	IA In	B.II.z	Change in pack size of the finished product	Addition of or change to a calendar package for a pack size already registered in the dossier.
Q	C.3.b	IB	C.I.3.z	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Article 45 or 46 of Regulation (EC) No 1901/2006, or the outcome of a PRAC signal recommendation, or to adapt to a joint recommendation of EU competent authorities (e.g., a Core SmPC, or following the assessment of an Urgent Safety Restriction etc.)	Implementation of the agreed wording that requires additional minor assessment, e.g., translations are not yet agreed upon.
Q	C.11	IB	C.I.z	Submission of results of assessments carried out on target patient groups in order to comply with Article 59(3) of Directive 2001/83/EC and any resulting change(s) to the Package Leaflet.	

What does the inclusion of Article 5 recommendations mean for applicants?

Practical Impact of integration in the Guidelines

Allows more consistent interpretation that ensures correct management of unforeseen variations.

Reduces discrepancies, misclassification, across Member States, streamlining regulatory processes for greater efficiency.

Enables **better harmonisation** throughout the EU.

Focus on **MA lifecycle**:

The Guidelines are continuously adapted to scientific advances, reducing the administrative burden.

Challenge and compliance obligations for Applicants

Classifications can change every year. **Applicants** must continuously **monitor EMA's annual recommendations**.

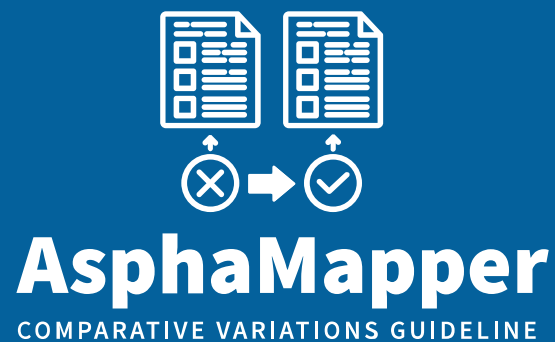
Applicants can more confidently determine the correct category for unlisted changes.

Applicants must review and adapt internal procedures quickly to comply with the correct category of the new classification.

A failure to apply the latest classification may result in incorrect variation submissions, invalidation, procedural delays or regulatory non-compliance

Do you need support with Variations?

Contact us:
info@asphalion.com



Check out our [AsphaMapper](#)
free tool and compare the
old and new EU Variations
Guidelines!